REMARKS

This amendment is intended to replace the amendment filed July 2, 2009, which was denied entry according to the Advisory Action of July 20, 2009. Accordingly, the present amendment is filed with a Request for Continued Examination, and includes arguments to respond to the remarks made in the Advisory Action.

Applicants thank Examiner Vakili for her time and consideration of the present application during the telephonic interview of May 7, 2009 with the undersigned.

During the interview, an amendment to claim 16 was proposed to focus the claim on specific mutant p53-mediated cancers that are specifically discussed in the specification. Although Applicants believe that such an amendment complies with the enablement requirement, Examiner Vakili would not agree to withdrawing the rejection at that time.

Status of the Claims

Claim 16 is amended to define specific mutant p53 mediated diseases, which include osteosarcoma, lung adenocarcinoma, Burkitt lymphoma, ovarian carcinoma and colon carcinoma.

Support for the amendment may be found generally throughout the specification, as described with respect to the enablement requirement discussed below.

Claims 16 and 18 remain in this application.

Claim Rejections-35 USC §112

Claims 16 and 18 were rejected under 35 U.S.C. §112, first paragraph, for not complying with the enablement requirement. This rejection is respectfully traversed for the reasons below.

The position of the Official Action was that the specification does not reasonably provide enablement for "treating all p53 mediated cancer" and further "treating other types of cancer in a mammalian subject".

However, claim 16 is now directed to a method of treating specific mutant p53 mediated diseases, which are selected from the group consisting of osteosarcoma, lung adenocarcinoma, Burkitt lymphoma, ovarian carcinoma and colon carcinoma.

The specification provides enablement for treating these specific mutant p53-mediated cancers, as experimental evidence in support of the claimed treatment method is disclosed throughout the specification, as discussed in detailed below:

Osteosarcoma

PRIMA-1, MIRA-1, as well as a series of compounds of formula (I) according to claim 1 were tested *in vitro* in the Saos-2-His 273 cell line, which is a human osteosarcoma cell line

carrying mutant p53, as described at **page 9** (of the originally filed application), i.e., **paragraph [0096]** (of the published US application) and **page 11, paragraph [0121].**

The results of these tests are illustrated in **Fig. 2A**, as described **at page 6, paragraph [0059]**, in **Figs. 12A-B** as described at **page 7, paragraph [0069]** and in the **table at pages 3-4** (just under paragraph [0043]).

Thus, **Figs 2A** and **12A-B** illustrate how MIRA-1 and PRIMA-1 suppressed the growth of osteosarcoma cells expressing mutant p53 but did not affect cells without p53 expression. In the table at pages 3-4, however, IC50 values for compounds according to formula (I) in the same osteosarcoma cell line are shown. Special attention also is drawn to the passage at **page 4, paragraph [0044]**, where it is noted that the compounds of formula (I) exhibit a specific activity towards mutant p53 *similar or greater* than that of PRIMA-1.

PRIMA-1 also was tested *in vivo*, using mice inoculated with human mutant p53 osteosarcoma cells, cf. **page 8, paragraph [0090]; page 11, paragraph [0119]** and **Fig. 11**, as described at **page 7, paragraph [0068].** The results show that PRIMA-1 also has an anti-tumor activity *in vivo*.

Thus, a method of treating osteosarcoma complies with the enablement requirement.

Lung adenocarcinoma

PRIMA-1, MIRA-1 and the compounds according to formula (I) of the present invention also were tested against the mutant p53 lung adenocarcinoma cell line H1299-His-175 as described at **page 9, paragraph [0096]** and **page 11, paragraph [0121].** The results of these tests are shown in **Fig. 2B**, as described **at page 6, paragraph [0059]** and in the **table at pages 3-4.** As may be noted, the results are substantially similar to those found with the osteosarcoma cell line, which indicate that the inventive compounds are also active against lung adenocarcinoma.

Thus, a method of treating lung adenocarcinoma meets with the enablement requirement.

Burkitt lymphoma

In vitro experiments on mutant p53 Burkitt lymphoma cell lines were performed using PRIMA-1 and MIRA-1; cf. **page 8, paragraph [0096],** where the mutant p53 Burkitt lymphoma cell lines used are identified as BL41 (Gln-248 mutant p53); DG75 (His-283), Raji (Gln-213, His-243), Ramos (Asp-254); and BJAB (Arg-193). The results, illustrated in **Fig. 7B**, as described at **page 7, paragraph [0064],** indicate that both PRIMA-1 and MIRA-1 are able to restore the sequence-specific DNA binding of the endogenous Trp-282 mutant p53 in cell extracts from Burkitt lymphoma. That there is a correlation between the restoration of the specific DNA binding and the apoptosis-inducing function of

mutant p53 is illustrated in **Fig. 8**, as described at **page 7**, **paragraph [0065]**.

Thus, a method of treating Burkitt lymphoma complies with the enablement requirement.

Ovarian carcinoma

In vitro experiments on mutant p53 ovarian carcinoma cells also were performed using PRIMA-1 and MIRA-1; cf. **page 8**, **paragraph [0096]**, where the mutant p53 ovarian carcinoma cell lines used are identified as SKOV-His-175 and SKOV-His-273. The results are illustrated in **Fig 2B**, as described at **page 6**, **paragraph [0059]**, which illustrates that both compounds show growth suppression effect on ovarian carcinoma cells in a mutant p53-dependent manner.

Thus, the specification does describe a method of treating ovarian carcinoma complies with the enablement requirement.

Colon carcinoma

In vitro experiments also were performed to show that both PRIMA-1 and MIRA-1 induced p53 target genes MDM2 and p21 in SW480 colon carcinoma cells carrying mutant p53, cf. **Fig. 10C** as described at **page 7**, **paragraph [0067]**.

Thus, a method of treating colon carcinoma complies with the enablement requirement.

In view of the above discussion, it is believed that the originally filed application, at the very least, contains an enabling disclosure for the present claimed method of treatment of a mutant p53 mediated cancer selected from the group consisting of osteosarcoma, lung adenocarcinoma, Burkitt lymphoma, ovarian carcinoma and colon carcinoma. That is, the original disclose shows that these diseases include the involvement of mutant p53, which is the common link between these disease.

It is further believed that the experiments described in the present application show that the restoration of the growth suppression function of mutant p53 does occur in the various cells.

Moreover, in general terms, the determination of the sequence of a gene, such as the p53 gene is a matter of routine experimentation. Thus, one of ordinary skill in the art would have been able to verify whether p53 is present or not in any given cancer patient, i.e., whether the cancer is mediated by mutant p53 or not.

Indeed, these cancers where mutant p53 is involved, other than those currently recited, could also be treated according to the claimed invention. However, in order to comply with the enablement requirement according to the outstanding Official Action, the claims only recite cancer diseases for which

the original disclosure provides tests on cell line representative of these diseases.

Therefore, the present claims meet with the enablement requirement, and withdrawal of the rejection is respectfully requested.

Conclusion

In view of the amendment to claim 16 and the foregoing remarks, this application is in condition for allowance at the time of the next Official Action. Allowance and passage to issue on that basis is respectfully requested.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our credit card which is being paid online simultaneously herewith for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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